

## **Pilot experience using drug provocation testing for the study of hypersensitivity to chemotherapy and biological agents**

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De-labelling is becoming paramount in drug allergy pathways[1]. However, data on de-labelling patients with reactions to chemotherapy and biologics is lacking, and it is limited to a few specialised centres with specific populations[2-4]. A recent publication that focused on using drug provocation testing (DPT) for de-labelling patients reacting to chemotherapy and biologics made us reconsider our local pathways[5].

Our centre has a longstanding experience with Rapid Drug Desensitisation (RDD), a technique that will allow patients to safely receive their treatment despite being allergic[6-7]. Receiving chemotherapy by means of RDD does not affect survival (i.e. does not affect the efficacy of the drugs) and is cost-effective[8-9]. However, an RDD will be needed for every administration of the drug, so these resource-intensive procedures tend to accumulate and trigger waiting lists. Thus, de-labelling patients with a favourable risk-assessment seems reasonable and efficient.

Our main objective was to audit our pilot experience after implementing DPT in the pathways of our Drug Desensitisation Centre (DDC), a multi-professional team with access to dedicated spaces that are fully integrated in a referral cancer centre. Our secondary objective was to monitor the activity of our DDC.

We performed a retrospective analysis of our database and we included all the patients referred to our DDC between January 2018 and March 2019 (15-month period). Ethics committee approval (PR165/20). All patients had documentation for their systematic clinical history, skin testing (ST) and DPT results, including

informed consents. Only patients reacting to intravenous drugs within 48 hours of administration were included.

Initial reactions were classified into immediate (occurring during drug infusion or within 1 hour after finishing) and nonimmediate (>1 hour after finishing drug infusion), and their severity was graded according to both Brown's classification and the Ramon y Cajal University Hospital's (RCUH's) classification[2,10]. Patients were then classified as low or high-risk patients, according to the RCUH recommendations[2].

ST, including skin prick testing (SPT) and intradermal testing (IDT), was performed according to standard operating procedures by the European Academy of Allergy and Clinical Immunology[11], following the recommended concentrations and safety measures for chemotherapy as per RCUH[2,6].

Low risk patients with a mild reaction and negative skin testing were offered DPT. Patients were empowered to make the final decision on DPT after a multidisciplinary team decision-making process in which the oncologist confirmed the indication and the allergist conducted the risk-assessment[2,12-13]. Concomitant drugs (other chemotherapy or biological agents, leucovorin, antiemetics, and so on) that could be involved in the reaction were studied separately with ST and DPT to confirm tolerance to them, but this was not included in the analysis[2,14].

Patients with a negative DPT were de-labelled and considered non-allergic. Patients with positive ST and/or positive DPT and/or a high-risk assessment were offered RDD[2,5,13]. For RDD we used the flexible standard protocols published by the Brigham and Women's Hospital (BWH)[9]. We studied concomitant drugs separately[5,14]. We used no additional premedication for RDD, but only the standard premedication for each drug as per institutional protocols for standard infusions[2,12,15]. In case of a reaction, we reassessed based on *in vivo* and *in vitro* biomarkers, and considered adding personalised adjustments to the second RDD (customised premedication or prophylactic drugs, decelerating dose escalation, additional solutions, or temporary dose reduction)[2].

Both DPT and RDD were carried out in a dedicated area within the inpatient infusion centre set up as the AllergoOncology Day Case Unit for these patients. This area is equipped with all the necessary resources for anaphylaxis, including rapid intensive care access, 1:2 nurse:patient ratio, and allergist at bedside[2,6].

During this 15 -month period 93 patients were referred to us (55 women and 38 men). All patients were suffering from malignancies, mainly colorectal cancer (29%), breast cancer (15%), ovarian cancer (13%), lung cancer (10%), cervical cancer (4%). See Figure 1 for data on culprit drugs. The initial reactions were mild in 38% (35/93) of the referred patients, and all of them were immediate.

ST was positive with the culprit drug in 43% of patients (40/93). Up to 67% (32/48) of platin-reactive patients had positive ST, with 24 oxaliplatin-positive patients (all in IDT, except for one SPT), seven carboplatin-positive patients (5 IDT, 2 SPT), and one positive IDT to cisplatin. Only four taxane-reactive patients had positive ST (three to paclitaxel and one to docetaxel), and there were three positive IDTs to rituximab, and one to cetuximab.

DPT was performed in 23 patients (25% of all referred patients). See Figure 1 for more data. Most DPTs (22/23) were negative, but only one DPT was positive in an oxaliplatin-reactive patient, who experienced a moderate reaction (grade 2 Brown, grade II RCUH) during DPT, and this was controlled as per protocol[2]. Despite the reaction during DPT, the patient received all their programmed medication that same day by means of the previously published 'restart protocol' [2,5-6], and was then progressed to RDD for the next programmed administration.

We performed a total of 378 RDDs in 71 patients (the 70 patients who did not undergo DPT plus the patient with a positive DPT) during this 15-month period, and they all successfully received all their prescribed treatments. We only found mild reactions in 6% (24/378) of the RDD procedures. Supplementary Figure 1 is a run chart that shows a shift in the number of RDD procedures after DPT implementation.

Thanks to our multi-professional DDC, 100% of all referred patients during this

15-month period were able to safely receive their first line therapy either by means of RDD or after a negative DPT. The BWH flexible standard RDD protocol was effective and safe in our population (with a higher representation of oxaliplatin-reactive patients than that of the BWH). The implementation of DPT helped de-labelling 24% (22/93) of all referred patients. Our very limited patient selection criteria for DPT (only very low risk patients with mild reactions) possibly underestimates the number of patients that could have been de-labelled if more patients had been included for DPT. Nevertheless, a 24% of de-labelled patients means saving a remarkable number of unnecessary resource-intensive RDDs (22 patients, with a mean number of 5 RDDs per patient, means that we have potentially saved 110 RDDs). These pilot data on the implementation of DPT have been surprisingly favourable, with only one patient suffering a moderate reaction, which should be easily controlled at any highly specialised allergy centre.

#### **Conflict of interest statement**

There are no potential conflicts of interest for any of the authors regarding this article.

#### **Financial sources statement**

There are no financial interests, and there have been not any provision of study materials by their manufacturer for free or at a discount from current rates.

#### **Additional disclosures**

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**Figure 1.** Flow chart for a pilot experience on implementing drug provocation testing to the allergy workup of chemotherapy and biological agents.

